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Published in:
Journal of the American Chemical Society

DOI:
10.1021/ja901961y

Publication date:
2009

J|A|C|S COMMUNICATIONS

Published on Web 06/01/2009

Iridium/Monodentate Phosphoramidite Catalyzed Asymmetric Hydrogenation of *N*-Aryl Imines

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Chiral amines are important synthetic intermediates in the preparation of many physiologically active compounds. One of the methods for their preparation is the asymmetric hydrogenation of C=N containing functional groups (imines, oximes, hydrazones, etc.). Despite some progress in the field, asymmetric hydrogenation of imines still represents major challenges. Although many highly efficient catalysts have been developed for the asymmetric hydrogenation of ketones and alkenes, much less examples have been reported for the metal-catalyzed asymmetric hydrogenation of imines with both high enantioselectivities and acceptable turnover frequencies.[1]

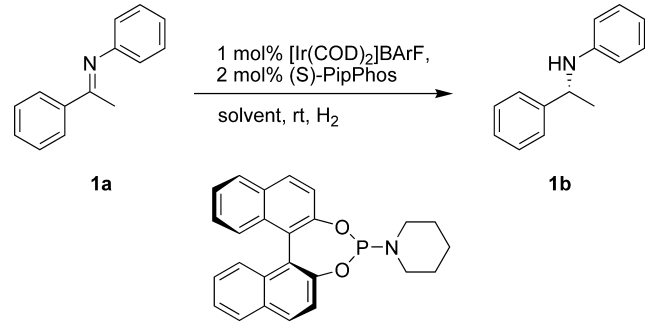
Bidentate chiral ligands were considered superior over monodentate ones in metal-catalyzed asymmetric hydrogenation for more than 30 years[2] as chelation was thought to be necessary to impart rigidity to the metal complex for an efficient transfer of chirality. Monodentate phosphoramidite ligands, however, have the advantage of being readily accessible, highly modular, air stable, and inexpensive compared to most bidentate ligands.[3] In addition, they are amenable to parallel synthesis.[4]

Recently, we reported the asymmetric hydrogenation of 2,6-substituted quinolines catalyzed by iridium complexes based on monodentate BINOL-derived phosphoramidites with high enantioselectivities.[5] Herein we report the highly enantioselective asymmetric hydrogenation of acyclic *N*-aryl imines using readily available (*S*)-PipPhos as chiral monodentate ligand.[6]

Asymmetric hydrogenation of *N*-phenyl-(1-phenyl-ethylidene)-amine (**1a**) was chosen as a model reaction. Initial hydrogenation experiments were performed to determine the optimal solvent and reaction conditions (Table 1). The reaction is strongly solvent dependent: in protic solvents such as methanol no reaction was observed (entry 4). Excellent conversions and high enantioselectivities (80 to 87%) were obtained in toluene and dichloromethane (entries 3, 6−8). It was also observed that pressures above 5 bar caused a slight decrease in enantioselectivity and shorter reaction times (19 h at 1 bar, 2 h at 25 bar, entries 6−8). An interesting anion effect was observed using different iridium precursors, with cationic $[Ir(COD)_2]BArF$ giving the best results.[7] High reaction rates were observed with $[Ir(COD)_2]PF_6$ (full conversion in 30 min); however the enantioselectivity remained at 65% (entries 9, 10). No conversion was observed using neutral $[Ir(COD)Cl]_2$ as catalyst precursor at rt and 5 bar; however at 50 bar and 60 °C the reaction goes to completion yielding the product amine with 61% ee (entries 11 and 12).

It is known that the nature of the substituent attached to nitrogen influences the properties of the C=N bond in terms of basicity, reduction potential, etc. Thus we examined the effect of substituents on the phenyl group in the asymmetric hydrogenation of *N*-phenyl acetophenone imine (Table 2). The introduction of 3,5-dimethyl groups on the aryl ring of the substrate led to excellent enantioselectivities upon hydrogenation of the imine (entries 4, 5). As we considered it essential to have an aryl group which can be easily removed to afford the primary amines, we examined the additional introduction of a methoxy group at the 2- and 4-positions of the *N*-aryl group. Indeed substrates **5a** and **6a** could be hydrogenated with 99% ee (entries 6−8). Although the rate of hydrogenation of trimethoxy-phenyl imine **5a** was very high, the imine was shown to be susceptible to hydrolysis thus giving reproducibility problems. Since amines behave as catalyst poison we assume that the presence of aniline was the cause of the irreproducibility.[8] As 3,5-dimethyl-4-methoxyaniline is fairly expensive we decided to test simple 2- and 4-anisidine based imines (entries 2, 3). Although the 4-methoxy-group had a remarkable negative influence on the enantioselectivity (amine **2b**), hydrogenation of the imine based on 2-anisidine gave

Table 1. Asymmetric Hydrogenation of *N*-Phenyl-(1-phenyl-ethylidene)-amine[a]



(S)-PipPhos

entry	solvent	metal precursor	P (bar)	conv.[b] (%)	ee[c,d] (%)
1	EtOAc	$[Ir(COD)_2]BArF$	5	14	77
2	acetone	$[Ir(COD)_2]BArF$	5	12	80
3	toluene	$[Ir(COD)_2]BArF$	5	99	87
4	MeOH	$[Ir(COD)_2]BArF$	5	0	−
5	THF	$[Ir(COD)_2]BArF$	5	18	60
6	DCM	$[Ir(COD)_2]BArF$	1	100	87
7	DCM	$[Ir(COD)_2]BArF$	5	100	80
8	DCM	$[Ir(COD)_2]BArF$	25	100	73
9	DCM	$[Ir(COD)_2]PF_6$	1	100	64
10	DCM	$[Ir(COD)_2]PF_6$	5	100	65
11	DCM	$[Ir(COD)Cl]_2$	5	0	−
12[e]	DCM	$[Ir(COD)Cl]_2$	50	100	61

[a] Reaction conditions: 1 mmol of substrate, 0.01 mmol of $[Ir(COD)_2]BArF$, 0.02 mmol of PipPhos, 4 mL of solvent at rt, 19 h. [b] Conversions were determined by ^1H NMR. [c] Ee was determined by GC. [d] Absolute configuration was determined by comparison of the optical rotation with literature (see Supporting Information, SI). [e] Reaction performed at 60 °C.

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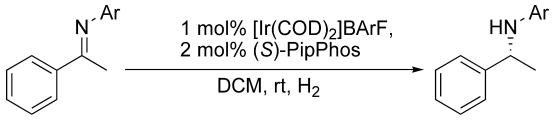
10.1021/ja901961y CCC: $40.75

Table 2. Influence of Phenyl Substituents on the ee in the Asymmetric Hydrogenation of *N*-Phenyl-(1-phenyl-ethylidene)-amine[a]



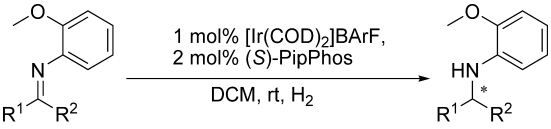
1-6a **1-6b**

entry	imine	Ar	pressure (bar)	time[b] (h)	ee[c] (%)	configuration[d]
1	**1a**	Ph	1	19	87	*R*
2	**2a**	4-MeO-Ph	5	3	71	*R*
3	**3a**	2-MeO-Ph	5	10	97	*R*
4	**4a**	3,5-$(CH_3)_2$-Ph	1	26	>99	*R*
5	**4a**	3,5-$(CH_3)_2$-Ph	5	4	>99	*R*
6	**5a**	3,4,5-$(OMe)_3$-Ph	1	6	99	–
7	**5a**	3,4,5-$(OMe)_3$-Ph	5	1.5	99	–
8	**6a**	3,5-$(CH_3)_2$, 4-MeO-Ph	5	10	99	–

[a] Reaction conditions: 1 mmol of substrate, 0.01 mmol of $[Ir(COD)_2]BArF$, 0.02 mmol of PipPhos, 4 mL of CH_2Cl_2 at rt. [b] Time to achieve full conversion. [c] Ee was determined by GC or HPLC. [d] Absolute configuration was determined by comparison of optical rotation with literature (see SI).

the product **3b** with 97% ee.[9] Thus we decided to test the scope of this class of imines. A range of imines with electron-donating and -withdrawing substituents on the aromatic ring were studied (Table 3). All tested substrates (except **13a** and **16a**) could be hydrogenated with excellent enantioselectivities (up to 99% ee, entry 2). Electron-donating or -withdrawing substituents in the 4-position gave comparable results (entries 4−7). We were pleasantly surprised to observe that the imines **14a** and **15a** were hydrogenated with excellent ee, even though these imines were isolated as a mixture of *syn* and *anti* isomers (entries 10, 11).

Table 3. Asymmetric Hydrogenation of *N*-2-MeO-phenyl Imines[a]



3a, 7a-16a **3b, 7b-16b**

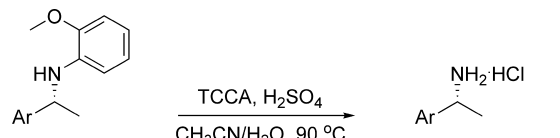
entry	imine	R^1	R^2	P (bar)	time[b] (h)	ee[c] (%)
1	**3a**	Ph	Me	5	10	97
2	**7a**	2-naphthyl	Me	1	11	99
3	**7a**	2-naphthyl	Me	5	6	97
4	**8a**	4-Me-Ph	Me	5	10	98
5	**9a**	4-Cl-Ph	Me	5	3	97
6	**10a**	4-CF_3-Ph	Me	5	6	97
7	**11a**	4-F-Ph	Me	5	6	97
8	**12a**	3-Me-Ph	Me	5	30	93
9	**13a**	3-NO_2-Ph	Me	5	0.2	61
10	**14a**	Ph	Et	5	19	94[d]
11	**15a**	Ph	Pr	5	20	97[d]
12	**16a**	*n*-butyl	Me	5	10	16[d]

[a] Reaction conditions: 1 mmol of substrate, 0.01 mmol of $[Ir(COD)_2]BArF$, 0.02 mmol of PipPhos, 4 mL of dichloromethane at rt. [b] Time to achieve full conversion. [c] Enantiomeric excess was determined by HPLC. [d] Imines prepared as mixture of *E*/*Z* isomers.

Asymmetric hydrogenation of 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline under the same conditions gave the product in 62% ee. *N*-*n*-Butyl-1-indanone imine was hydrogenated with 40% ee.

Deprotection of the 2-methoxy-phenyl amines went smoothly using trichloroisocyanuric acid as the oxidant (Scheme 1).[10]

Scheme 1. Deprotection of the *N*-Anisidyl Amines



3b, Ar = Ph, 97% *ee*
7b, Ar = naphthyl, 99% *ee*

(*R*)-**3c**, 97% *ee*
(*R*)-**7c**, 99% *ee*

Reactions were performed in a mixture of acetonitrile and water in the presence of H_2SO_4, giving the desired primary amine in acceptable yield (70%) and preserving the stereochemical integrity. This yield was comparable with the known CAN (cerium ammonium nitrate) removal of the 2-methoxy substituted *N*-phenyl group.[11] This deprotection also proceeds with bleach at rt, giving the primary amine in 51% yield.

In conclusion, we have developed a new low pressure hydrogenation method for a range of acyclic *N*-aryl imines with excellent enantioselectivities, using an *in situ* prepared iridium catalyst based on the cheap monodentate ligand PipPhos.

Acknowledgment. We thank Umicore for a generous gift of $[Ir(COD)_2]BArF$. We thank A. Kiewiet, T. Tiemersma-Wegman, and M. de Vries (U. of Groningen) for technical support.

Supporting Information Available: NMR spectra, the experimental procedures, and HPLC and GC methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA901961Y